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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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RE: Comments to FDA Docket No. 98D-1146, Draft Guidance for Industry #152 "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern"

Elanco Animal Health, a Division of Eli Lilly and Company, provides these comments on the FDA Center for Veterinary Medicine (CVM) Draft Guidance document #152 to assess the microbiological safety of antimicrobial agents used in food producing animals. Elanco Animal Health is a research-based company engaged in bringing innovative, safe and effective animal health products to the marketplace.

Elanco offers the following comments in the spirit of seeking to advance public health, food safety, animal health and animal welfare as regulatory criteria are modified and refined for assessing the microbiological safety of antimicrobial agents used in food animals. Considering our scientific knowledge of the macrolide antibiotics, these comments reference the macrolide class of compounds as an example for modifications to the overall categorization approach of antibiotics. Macrolide antibiotics are important for veterinary medicine so it is critical that the food consumer has confidence regarding their safety as it is determined within the approach defined by Draft Guidance 152.

First, we agree with the CVM that foodborne pathogens should be the sole focus of the microbiological safety assessment as this is the primary path of resistance transfer regarding antibiotic use in animals. Second, following this basis, we propose that the initial categorization be based on the foodborne disease pathogen and the respective species use of the product. Third, the assessment should look at specific foodborne disease pathogens in regards to resistance characteristics, and not the indicator organisms or resistant genes, as the pathogen is the primary carrier that could impact food safety or

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public health. Finally, for those antibiotic compounds, or class of antibiotic compounds, with no approved use in human medicine, and limited or no concern regarding foodborne pathogen transfer, they should be considered "negligible risk" and thus assigned a low or even "negligible" categorization.

The FDA/CVM regulatory process is designed to ensure that stringent public health standards and criteria are used for product approvals. New evaluation criteria should be transparent for all stakeholders, as they are important in ensuring that safe and effective drugs can be brought to the marketplace to enhance the health and welfare of animals and also enhance the safety of animal-derived food. Specifically, we believe that the process used to rank the macrolide antibiotic class as of "High" importance to human medicine does not provide sufficient transparency on how this determination was made, and inappropriately ranks the re-evaluation of macrolides in Appendix C based on the categorization listed in Appendix A. Unfortunately, as published, the draft guidance only provides human use as the basis for ranking of the macrolides and thus discourages all animal uses and further product developments.

Elanco Animal Health believes that the present "High" ranking of the macrolide class of antibiotics is inappropriate and should instead be categorized as "Low" based on the following reasons:

1. Foodborne disease pathogen: The main zoonotic pathogens of concern are salmonella and campylobacter. Macrolides are not active against salmonella, but are used to treat diagnosed cases of systemic human campylobacteriosis (for non-systemic infections either no antibiotic is prescribed or empiric therapy with a fluoroquinolone is given). Although enterococci may contaminate food products, they do not cause a foodborne disease if ingested by humans. Hypothetical transfer of resistance genes, such as *erm* genes, to non-intestinal human pathogens (e.g. *Legionella pneumophila* as cited in the draft) remains to be shown to occur, let alone contribute to, impaired human disease treatment with macrolides. The Sandford Guide lists several indications for human disease treatment with macrolides, but not enterococcal disease (Gilbert, DN, RC Moellering, MA Sande. 2002. Sanford guide to antimicrobial theray, 32nd ed. Antimicrobial Therapy, Inc., Hyde Park, VT).
2. Pathogen and animal species impact: The U.S. NARMS program has accumulated resistance monitoring data on azithromycin and erythromycin (macrolides) resistance in campylobacter isolates from humans. (Website: http://www.cdc.gov/narms/annual/2000/figures/figure_18.htm). The prevalence of resistance remains very low and stable over the last three years at ~2%. In animals, resistance prevalence varies for *C. jejuni* with very low frequency of

<1% in recent years and for *C. coli* of 14-22% (Website: http://www.arru.saa.ars.usda.gov/campy/summary_campylobacter.pdf). Thus, adequate monitoring data from NARMS has been collected and shows that macrolide resistance in campylobacter is not worthy of a "High" designation in Appendix A.

3. Resistance characteristics: Cross-resistance with other macrolides, lincosamides, and streptogramin b is a known fact. However, streptogramins are not used to treat foodborne disease, nor are they targeted to salmonella or campylobacter. Lincosamides have a secondary indication for campylobacter. Moreover, macrolide resistance in campylobacter has not been conclusively shown to be mediated by anything other than a target site mutation, thereby minimizing the potential for resistance dissemination (Engberg J, FM Aarestrup, DE Taylor, P Gerner-Smidt and I Nachamkin. 2001 Quinolone and Macrolide Resistance in *Campylobacter jejuni* and *C. coli*: Resistance Mechanisms and Trends in Human Isolates Emerging Infect Dis 7. Jan-Feb. www.cdc.gov/ncidod/eid/vol7no1/engberg.htm and Yan W., Taylor D. 1991. Characterization of Erythromycin Resistance in *Campylobacter jejuni* and *Campylobacter coli*. Antimicrobial Agents and Chemotherapy, 1989-1996).

Additional microbiological discussion can be provided in the future, and can also be found in the comments submitted by the Animal Health Institute, of which Elanco Animal Health is a member. However, Elanco believed it was necessary to address the specific inappropriate ranking of macrolides in the draft Guidance to help reassure consumers, producers, and also our customers, of the safety of macrolide products used in food animal medicine.

Stringent regulatory standards that provide for the development and approval of antibiotics for food animal use is critical. Antibiotic product approvals will allow farmers and veterinarians the ability to produce healthy animals and safe food products. We look forward to working with the FDA to improve the draft Guidance 152 to meet our common goal of quality, safety, and effectiveness for animal health products.

Sincerely yours,

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